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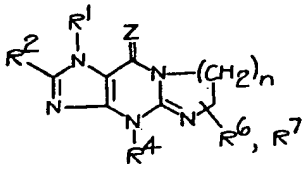
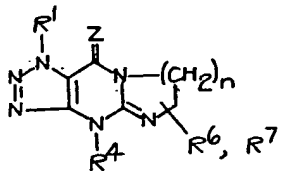
## (54) HETEROCYCLOPYRIMIDINES, COMPOSITIONS, AND THERAPEUTIC PROCESS


(71) We, BRISTOL-MYERS COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, having offices located at 345 Park Avenue, New York, New York, 10022, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:-


This invention is concerned with aminopyrimidine compounds having a fused heterocyclic ring on the pyrimidine ring. It is also concerned with drug, bio-affecting and body treating compositions containing these heterocyclic pyrimidine compounds.

The compounds of the present invention are shown by Formulas I and II





In these formulas, $R^1$ is hydrogen or the group A wherein A is an alkyl or alkenyl group each having up to 8 carbon atoms, pyridylmethyl, aralkyl having 7 to 12 carbon atoms, substituted aralkyl having 7 to 12 carbon atoms, aryloxyalkyl having 8 to 12 carbon atoms, or substituted aryloxyalkyl having 8 to 12 carbon atoms wherein each of said substituted aralkyl, and substituted aryloxyalkyl groups contain 1 or 2 ring substituents selected from halogen, alkoxy, and alkyl, and each of said alkoxy and alkyl groups contains up to 6 carbon atoms. $R^2$ is hydrogen, trifluoromethyl, halogen (fluorine, chlorine, bromine, iodine), azido, cyano, amino, or lower alkylamino, dialkylamino, or alkyl wherein each of said alkyl groups has up to 8 carbon atoms. $R^4$ is hydrogen, alkyl or alkenyl having up to 8 carbon atoms, pyridylmethyl, alkanoyl or alkenoyl each having up to 8 carbon atoms, aroyl having 7 to 10 carbon atoms, substituted aroyl having 7 to 12 carbon atoms, aralkyl having 7 to 12 carbon atoms, substituted aralkyl having 7 to 12 carbon atoms, aryloxyalkyl having 8 to 12

carbon atoms, or substituted aryloxyalkyl having 8 to 12 carbon atoms wherein each of said substituted aroyl, substituted aralkyl, and substituted aryloxyalkyl groups contains one or two ring substituents selected from halogen, alkoxy, and alkyl wherein each of said alkoxy and alkyl groups contains up to 6 carbon atoms. Bronchodilator compounds have $R^1$ and $R^2$ preferably hydrogen, and $R^4$ is preferably a substituted benzyl group, and most preferably a halobenzyl group such as 4-chlorobenzyl. $R^6$ and $R^7$ are hydrogen, methyl, or ethyl, and represent carbon attached ring substituents. Attachment at any of the ring carbon atoms is intended. *n* is the integer 1, 2, or 3. Z is the oxo (=O), or imino (=NH) group.

The compounds of Formulas I and II are bases and form salts with acids. The invention includes not only the substances of Formulas I and II but also the acid addition salts thereof. The pharmaceutically acceptable acid addition salts are those in which the anion does not contribute significantly to the toxicity or pharmacological activity of the salt and, as such, they are the pharmacological equivalents of the bases of Formulas I and II. They are preferred for medical usage. In some instances they have physical properties which make them more desirable for pharmaceutical formulation purposes such as solubility, lack of hygroscopicity, compressability with respect to tablet formation and compatibility with other ingredients with which the substances may be used for pharmaceutical purposes. The salts are made by reaction of a base of Formula I or Formula II with an acid, preferably by contact in solution. They may also be made by metathesis or treatment with an ion exchange resin under conditions in which the anion of one salt of the substance of the Formula I or Formula II is replaced by the anion of another under conditions which allow for separation of the undesired species such as by precipitation from solution or extraction into a solvent, or elution from or retention on an ion exchange resin. Pharmaceutically acceptable acids for the purposes of salt formation of the substances of Formula I and II include hydrochloric, hydrobromic, hydroiodic, citric, acetic, benzoic, phosphoric, nitric, mucic, isethionic, glucosaccharic, palmitic and heptanoic acids.

The substances of Formula I and Formula II wherein $R^1$ is hydrogen are amphoteric and also form salts with bases. Accordingly, the pharmaceutically acceptable metal, ammonium and amine salts of the substances of Formulas I and II wherein $R^1$ is hydrogen are included within the present invention. Again, the definition of a pharmaceutically acceptable salt is substantially in accord with the foregoing discussion of pharmaceutically acceptable acid addition salts, but in this instance it is the cation which makes no significant contribution to toxicity or pharmacological activity. The cationic portion of these salts generally contributes to the utility of these active ingredients as the result of the physical properties of the salt for pharmaceutical reasons. The salts may be prepared as in the case of the acid addition salts by reaction of the substance of Formula I or Formula II wherein $R^1$ is H with the base, preferably in solution in a reaction inert liquid medium or they can be prepared by metathesis or treatment with an ion exchange resin under conditions whereby the cation of one salt of substance of Formula I or II is replaced by another cation and the undesired species is eliminated, for instance by precipitation from solution or extraction into a solvent, or elution from or retention on an ion exchange resin. Suitable metal salts include the sodium, potassium, calcium, barium, magnesium, aluminium, and zinc salts. Similarly, the ammonium and amine salts are also considered part of the invention, these salts being prepared in substantially the same way as the metal salts from appropriate starting materials. Ammonia, ammonium hydroxide, ammonium salts, various amines, amine salts or quaternary ammonium salts and hyroxides may be employed as reactants. Suitable types of amines include:

(a) primary, secondary or tertiary alkyl and alkenyl amines having up to 22 carbon atoms and up to 3 carbon-carbon double bonds;

(b) hydroxy substituted primary, secondary, and tertiary alkyl amines having from 1 to 22 carbon atoms and up to 3 hydroxyl groups;

(c) the alkylenediamines having from 1 to 6 carbon atoms; and

(d) the heterocyclic amines having from 3 to 10 carbon atoms and from 1 to 3 heteroatoms of which at least one is nitrogen.

Preferred amine salts are those of the alkylamines having up to 6 carbon atoms or hydroxy substituted alkylamines having up to 6 carbon atoms and 3 hydroxyl groups and the alkylenediamines having 2 to 4 carbon atoms. Suitable amines include ethylenediamine, triethylamine, tris(2-hydroxyethyl)amine, 2-hydroxyethylamine and piperidine.

Compounds of Formula I and Formula II are useful as bronchodilators, antiallergy agents in the inhibition of the immediate hypersensitivity reaction, as vasodilators, and as inhibitors of the enzyme phosphodiesterase. The invention includes processes for the treatment of non-human mammals requiring bronchodilation, vasodilation, or having allergy with a non-toxic bronchodilator effective, vasodilator effective, or immediate hypersensitivity reaction inhibiting dose of one of these compounds. The compounds may be administered orally, parenterally, topically by inhalation, or rectally. Effective doses

range from 0.03 mg./kg. of body weight up to the maximum non-toxic dose which can be administered without undue side effects. Maximum non-toxic doses can be determined by standard pharmacologic techniques using mice. The value for the substance produced by procedures 3 or 4 herein, a preferred compound for anti-asthma use, is about 250 mg./kg. of body weight *per os* in mice.

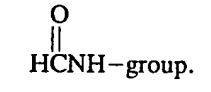
The invention therefore also includes pharmaceutical compositions comprising a compound according to the invention and a pharmaceutical diluent or carrier.

Compounds of Formulas I and II and their salts are believed to inhibit the degranulation of sensitized mast cells. Immediate hypersensitivity reactions such as asthma, hay fever, allergic rhinitis, urticaria, and food allergy are believed to be mediated by reaction of immunoglobulin E, sometimes referred to as reaginic antibody, with an antigen on the cell membrane of a mast cell to initiate reactions within the mast cell which ultimately release mediators such as bradykinin, histamine, serotonin or slow reacting substance-A (SRS-A). The mediators effect changes in end organs such as airways, blood vessels, skin, and mucus membranes resulting in the symptoms of an allergic attack. The present substances are believed to prevent the release of mediators thereby preventing the allergic attack. They are, therefore, useful in the prophylactic treatment of subjects possessing hypersensitivities of the foregoing types, and inhibit acute allergic attacks such as asthma, hay fever, allergic rhinitis, urticaria, and food allergy. Preferred compounds are distinguished particularly by the fact that they are orally active, have very low toxicities, and have bronchodilator action. They are thus useful in treating asthmatic attacks as well as prophylactically for hypersensitive subjects including those whose hypersensitivity is manifested by asthma. The compounds are inhibitors of rat lung phosphodiesterase, and they are peripheral vasodilators. Preferred compounds have vasodilator capacity comparable to papaverine in the dog perfused hind limb preparation.

Preferred compounds for anti-allergy and anti-asthma treatment are those substances of Formula I wherein $R^4$ is the substituted aralkyl group, more preferably the halobenzyl group, and most preferably those wherein $R^4$ is the halobenzyl group and $R^1$ and $R^2$ are hydrogen. These substances are orally effective hypersensitivity reaction inhibitors and bronchodilators having a long duration of action. A preferred species is 4-[(4-chlorophenyl)methyl]-6,7-dihydro-3*H*-imidazo[1,2-*a*]purin-9(4*H*)-one (Procedure 3 herein) which is more potent than aminophylline in anti-hypersensitivity and bronchodilator action, has a longer duration of action, and has reduced side effects such as central nervous system stimulation. This substance may be used for bronchodilator purposes in much the same manner as aminophylline, taking into consideration the increased potency and longer duration of action thereof. Oral or parenteral doses in the range of 0.03 to 250 mg./kg. of this substance may be employed. In man, the estimated effective single dose is in the range of from 10-500 mg. orally and might be given from 2 to 6 times a day. The substance may also be administered topically to the airways with a suitable device at a single dose in man of from 20-200 mg. given 2 to 6 times a day. Similar dosage regimens are also applicable for use thereof as an antihypersensitivity agent in asthma or allergic rhinitis.

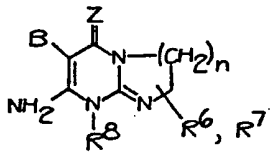
In the activity cage test using the mouse dosed orally, the substance of Procedure 3 exerted neither a stimulant nor a depressant action at doses of 10, 20, 40, 80, or 160 mg./kg. of body weight while aminophylline in the same test exhibited stimulation at doses of 15, 30, and 60 mg./kg. of body weight. The effective antihypersensitivity dose ($ED_{50}$) in the rat treated orally in the passive cutaneous anaphylaxis test of the substance of Procedure 3 is 34 mg./kg. of body weight and for aminophylline about 60 mg./kg. of body weight. The hypersensitivity inhibitory effect of the substance of Procedure 3 was sustained for a period in excess of 6 hrs. while that of aminophylline diminished to a non-significant level within 6 hrs. The bronchodilator action as measured *in vitro* by means of the guinea pig tracheal spiral ($IC_{50}$, concentration yielding 50% relaxation of the spontaneous tonus) for the compound of Procedure 3 is 14 mcg./ml. and for aminophylline 19 mcg./ml.

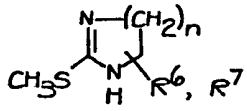
The key intermediates in the preparation of the compounds of Formula I and Formula II are the substances shown by Formula III in which B is hydrogen or the ON−, $H_2N$−, or



Certain compounds of Formula III exhibit blocking or stimulating action on smooth muscle, e.g., 7-amino-8-[(4-chlorophenyl)methyl]-6-formylamino-2,3-dihydroimidazo-[1,2-*a*]pyrimidin-5(8*H*)-one, and 7-amino-2,3-dihydro-6-nitroso-8-(2-phenoxyethyl)-imidazo[1,2-*a*]pyrimidin-5-(8*H*)-one. Those in which B is hydrogen or the ON-group are

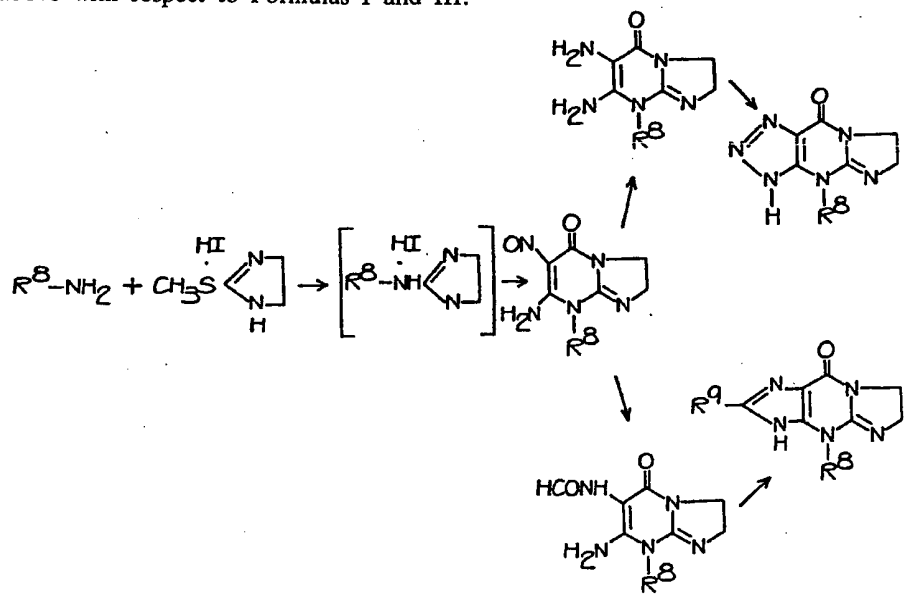
prepared from $R^6$, $R^7$, substituted 2-methylmercaptoimidazolines, 2-methylmercapto-3,4,5,6-tetrahydropyrimidines, or 2-methylmercapto-3,4,5,6-tetrahydro-1,3-diazepines, represented by Formula IV, by reaction thereof in the presence of base with ethyl cyanoacetate, ethyl oximinocyanoacetate, malonitrile, or oximinomalononitrile. The latter two reactants yield the intermediates in which Z is imino. In Formulas III and IV, $n$, Z, $R^6$ and $R^7$ have the same meanings is given above. $R^8$ in Formula III has the same meaning as $R^1$ in Formula I.





The intermediates of Formula IV are prepared according to known processes by the reaction of carbon disulfide with the appropriately substituted ethylenediamine, trimethylenediamine or tetramethylenediamine followed by etherification of the resulting 2-mercaptoimidazoline, 2-mercapto-3,4,5,6-tetrahydropyrimidine or 2-mercapto-4,5,6,7-tetrahydro-1*H*-1,3-diazepine.

The following discussion of the process for the synthesis of the substances of Formula I and Formula II is directed principally to those substances wherein $n$ is 1, and $R^6$ and $R^7$ are hydrogen. Nevertheless, the method is equally applicable to all members of the series. The process is shown schematically below. $R^1$ and $R^8$ have the same meanings as described above with respect to Formulas I and III.



Ammonia or a primary amine, is reacted with 2-methyl-mercaptoimidazoline to yield a 2-aminoimidazoline in which the amino substitutent has the formula $R^8NH-$. The latter, preferably without isolation, is then reacted in a condensation reaction with ethyl oximinocyanoacetate to give a 7-amino-2,3-dihydro-8-$R^8$-6-nitrosoimidazo[1,2-*a*]-pyrimidin-5(8*H*)-one, shown by Formula V in the reaction scheme, which is the intermediate of Formula III wherein B is ON−, Z is oxo, $n$ is 1, and $R^6$ and $R^7$ are hydrogen. The condensation reaction is carried out under anhydrous conditions in an anhydrous reaction inert liquid medium in the presence of a strong base which is capable of forming the anion of the aminoimidazoline intermediate. When using a lower alkanol such as ethanol, isopropanol, or butanol as solvent, sodium ethoxide or potassium *tert.*-butoxide is a satisfactory base. Other alkali metal alkoxides, amides, or hydrides may be employed such as sodium amide with liquid ammonia or an aprotic liquid medium, and sodium hydride with liquid ammonia or an aprotic liquid medium, and sodium hydride in an aprotic

liquid medium. The reaction produces the intermediates of Formula V in high yields of from 75 to 100% when $R^8$ is aralkyl or substituted aralkyl. An alternaive procedure and one which is preferred when $R^8$ is an alkyl or alkenyl group is to employ ethyl cyanoacetate as reactant rather than ethyl oximinocyanoacetate. The resulting 7-amino-2,3-dihydro-8-$R^8$-imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (Formula III, B, $R^6$, $R^7$ = H, $n$ = 1, Z = oxo) is then nitrosated with sodium nitrite in aqueous acetic acid to yield the intermediates of Formula V.

For the preparation of the substances of Formula I, the second step in the process involves reductive formylation of the nitroso group of the subtance of Formula V to yield the monoformylated diamino substance of Formula VI, which is the intermediate of Formula III werein B is HCOHN−, Z is oxo, $n$ is 1, and $R^6$ and $R^7$ are hydrogen. The reductive formylation is carried out in formic acid as reaction medium using either catalytic reduction employing a palladium supported on carbon catalyst or sodium dithionite as reducing agent. This operation involves dissolving the nitroso compound of Formula V preferably in 97% formic acid which may require from 10 ml. to 30 ml. of 97% formic acid per gram of substance of Formula V. Other equivalent formylating reaction media may be employed. When employing catalytic hydrogenation, hydrogen pressures of from atmospheric pressure up to 100 p.s.i. are satisfactory employing sufficient palladium supported on carbon catalyst to bring the hydrogenation to completion. A previously calibrated apparatus is convenient so that the extent of hydrogen absorption on a molecular basis can be measured. If the calculated quantity of hydrogen is not consumed before hydrogen absorption ceases, a fresh portion of catalyst is added and the hydrogenation is continued. The hydrogenation is carried out at room temperature although the process is exothermic resulting in a slight to moderate elevation in temperature depending on the batch size during the initial stages of hydrogenation. Temperatures to 20°C. to 40°C. are satisfactory. Hydrogenation usually requires a fairly short period of time of from 15 minutes to 1 hour depending upon the size of the batch and the particular apparatus employed.

When using sodium dithionite ($Na_2S_2O_4$) as reducing agent in the reductive formylation, it is simply added to a solution of the intermediate of Formula V in concentrated aqueous (87-97% by weight) formic acid. Somewhat more than a stoichiometric quantity is employed, but large excesses are not necessary since the reduction takes place more quickly than does the decomposition of the sodium dithionite. For reduction of an aromatic nitroso compound to the corresponding aromatic amino compound, two molecular proportions of sodium dithionite is a stoichiometric quantity. This is a novel and surprising process in view of the fact that the prior art has employed this reducing agent in basic solution only. Sodium dithionite is known to be decomposed in acidic media. Some sulphur is produced as a by-product during the reaction. The process is generally applicable to the reduction of aromatic nitroso compounds of the formula ArNO to aromatic amines of the formula $ArNH_2$ wherein Ar is an aromatic carbocyclic or an aromatic heterocyclic group.

Cyclization of the formyl diaminoimidazopyrimidinone of Formula VI to the 4-$R^8$-6,7-dihydro-2-$R^9$-3*H*-imidazo[1,2-*a*]purin-9(4*H*)-one of Formula VII is achieved either by heat alone or under the agency of a dehydrating agent such as polyphosphoric acid or an anhydride. The latter may also serve as a reagent for introducing the 2-$R^9$ substituent into the substances of Formula VII by means of an acyl interchange with the formyl group during the cyclization process. When employing an anhydride of the formula $(R^9CO)_2O$ in which $R^9$ is alkyl of 1 to 8 carbon atoms or trifluoromethyl as cyclization or dehydrating agent in the presence of pyridine as reaction medium, the $R^9$ substituent corresponding to the anhydride is introduced. For instance, isobutyric anhydride yields a 2-isopropyl substituted product, and trifluoroacetic anhydride yields the 2-trifluoromethyl product. The reaction is preferably carried out at the reflux temperature of the reaction mixture or within the range of 130°C. to 170°C. employing convenient solvent amounts of anhydride and pyridine relative to the amount of Formula VI intermediate being converted, but at least one molecular proportion of anhydride.

For pyrolytic cyclization of the formylamino compound of Formula VI to the product of Formula VII wherein $R^9$ is hydrogen, a temperature of about 260°C. is employed after diluting the intermediate of Formula VI with sufficient dimethylformamide to afford a fluid, non-viscous liquid on heating. The diluent is removed by evaporation during the process and results in the formation of the desired product as a residual cake which is usually brown in color. Alternatively, for the cyclization to yield substances of Formula VII, $R^9$=H, triethyl orthoformate may be used in combination with an alkanoic acid anhydride dehydrating agent. The triethyl orthoformate suppresses the acyl interchange reaction which occurs when the anhydride is employed with pyridine. Nevertheless, the product is sometimes contaminated with low percentages of the 2-$R^9$ substituted product from the anhydride $(R^9CO)_2O$. A convenient solvent amount of a liquid anhydride is employed in combination with approximately 2 to 5 molecular proportions of triethyl

orthoformate per molecular proportion of formylamino derivative. Again, the process is carried out at the reflux temperature or within the range of 130°C. to 170°C.

For the preparation of the substances of Formula I in which $R^4$ is alkanoyl, aroyl, or substituted aroyl one convenient method is to employ the intermediate of Formula VI wherein $R^8$ is a hydrogen atom and to employ the desired alkanoic, aroic, or substituted aroic acid anhydride as dehydrating or cyclizing agent in the transformation of the intermediate of Formula VI to the product of Formula VII as is described above. When pyridine is used as vehicle an $R^9$ substituent corresponding to the anhydride employed is also introduced. Similar conditions to those described above are employed. For instance, when 7-amino-6-formylamino-2,3-dihydroimidazo-[1,2-*a*]pyrimidin-5(8*H*)-one is refluxed with equal volumes of pyridine and isobutyric anhydride 6,7-dihydro-2-(1-methyl-ethyl)-4-(2-methylpropionyl)-3*H*-imidazo-[1,2-*a*]-purin-9(4*H*)-one is produced.

A substance of Formulas I or II wherein $R^4$ is H may be acylated in conventional fashion for the preparation of alkanoamides, arylcarboxamides, or ring-substituted arylcarboxamides using the corresponding carboxylic acid halide, anhydride, or mixed anhydride. Preferred conditions are those comparable to those known to be efficient for acylation of a weakly basic aniline derivative. In any given example, a determination should be made as to whether the $N^4-$ (Formula I or II wherein $R^4$ is alkanoyl, aroyl, or substituted aroyl) or $N^5-$acyl product is produced.

The products of Formula I and Formula II wherein $R^1$ is other than hydrogen are readily prepared by reaction of an alkali metal salt of a substance of Formula I or Formula II wherein $R^1$ is a hydrogen atom with a reagent of the formula AX wherein A has the same meaning given above, and X is a reactive ester group such as chloride, bromide, iodide, phosphate, or sulfate. The required alkali metal salt is obtained by reaction of the substance of Formula I, $R^1$ = H, with a strong alkali metal base in the reaction inert organic solvent such as an aromatic or aliphatic hydrocarbon, ether, alcohol, or amide such as dimethylformamide. Suitable bases include sodium hydride, sodium methoxide, potassium *tert.*-butoxide, sodium amide, or lithium hydride. Suitable reactive esters include butyl bromide, methyl iodide, dimethyl sulfate, triethyl phosphate, hexyl bromide, *tert.*-butyl chloride, benzyl bromide, 2-phenoxyethyl chloride, 4-fluorobenzyl bromide, 3-chlorobenzyl bromide, and 2-methoxybenzyl chloride. An elevated temperature in the range of 80 to 150°C. is desirable.

The compounds of Formula I wherein $R^2$ is hydrogen are subject to halogenation under conventional conditions for introduction of a chlorine, bromine, or iodine atom to yield the substances of Formula I wherein $R^2$ is chlorine, bromine, or iodine. For instance, treatment of an acetic acid solution of a product of Formula I wherein $R^2$ is hydrogen with elemental bromine results in introduction of a bromine atom into the 2-position. N-Bromosuccinimide, N-chlorosuccinimide or N-chloroacetamide may also be employed for halogenation. Other suitable halogenating agents and conditions include phosphorus oxychloride or phosphorus tribromide for conversion of a 2-hydroxy group to the corresponding 2-chloro or 2-bromo compound. The 2-chloro compounds may be converted to 2-iodo or 2-fluoro compounds by reaction with concentrated (47%) aqueous HI at 0°C. or conversion to the trimethylammonium salt followed by reaction of that product with $KHF_2$ at 50°C. in the absence of any diluent.

The 4-substituted 6,7-dihydro-3H-imidazo-[2'1':5,6]-*v*-triazolo-[4,5-*d*]-pyrimidin-9(4*H*)-ones of Formula II are produced from the intermediates of Formula V by reduction of the nitroso group to an amino group as shown in the compound of Formula VIII in the above reaction scheme which is the intermediate of Formula III wherein B is $H_2N-$, Z is oxo, *n* is 1, and $R^6$ and $R^7$ are hydrogen. The reduction may be carried out in a fashion similar to the reductive formylation in the production of the intermediates of Formula VI except that formic acid is replaced by some other reaction medium which is inert under the reaction conditions. For catalytic reduction an acidic medium is preferred and an aqueous mineral acid is quite satisfactory as reaction medium. Dilute aqueous hydrochloric acid is preferred. Other methods known to those skilled in the art for reduction of a nitroso group to an amino group are also applicable. The resulting diamino intermediate of Formula VIII is then converted to the product of Formula IX by treatment under conditions usually employed for the diazotization of aromatic amines, for instance sodium nitrite and aqueous hydrochloric acid. Isolation and purification of the intermediates of Formula VIII is not necessary. The solution resulting from reduction after separation of the catalyst may be treated with an aqueous solution of sodium nitrite and then simply evaporated to afford the desired product which is then purified by recrystallization.

To summarize, there is provided according to the present invention a process for the preparation of compounds of Formula I and Formula II which comprises first, forming the aminopyrimidine compound of Formula III wherein B is hydrogen or the ON− group, by condensation of malononitrile, oximinomalonitrile, or a lower alkyl ester of cyanoacetic

acid or oximinocyanoacetic acid, respectively, with a 2-$R^8$NH-1,3-diazocycloalk-2-ene and thereafter introducing the nitroso group by reaction of the product with nitrous acid when cyanoacetic ester or malononitrile is used as reactant, and then reducing the nitroso compound of Formula III (B is ON−) under formylating conditions when a compound of Formula I is desired and under non-formylating conditions when a compound of Formula II is desired, respectively yielding the monoformyldiaminopyrimidine of Formula III wherein B is the HCONH− group or the diaminopyrimidine of Formula III wherein B is the $H_2N$− group and thereafter cyclizing said compound of Formula III (B is $H_2N$− or HCONH−) to yield a compound of Formula I or a compound of Formula II wherein said cyclization in the preparation of Formula I compounds is carried out by heating said substance of Formula III (B = HCONH−) at a temperature of about 260°C. in the presence of sufficient of a reaction inert diluent to afford a liquid reaction mixture or alternatively heating said substance in the presence of a cyclodehydrating agent such as polyphosphoric acid or carboxyclic acid anhydride at a temperature within the range of 130°C. to 170°C. and wherein said cyclization in the preparation of Formula II compounds is carried out by diazotizing said substance of Formula III (B is $NH_2$) by treating with a diazotizing reagent under conditions which are known to be operable for the diazotization of aromatic amines, and thereafter when a compound of Formula I or Formula II is desired having $R^4$ alkanoyl, aroyl, or substituted aroyl reacting a substance of Formula I or II wherein $R^4$ is hydrogen with an acylating agent capable of introducing said alkanoyl, aroyl, or substituted aroyl group under conditions known for the production of amides from aromatic amines. Compounds of Formula I wherein $R^2$ is a hydrogen atom may be treated with a halogenating agent known to be suitable for introduction of a chlorine or bromine atom into an aromatic compound to produce a substance of Formula I wherein $R^2$ is chlorine or bromine and converting said chloro, or bromo compound to the corresponding fluoro, or iodo compound. Further, substances of Formulas I or II wherein $R^1$ is hydrogen may be converted to an alkali metal salt by treatment with a strong alkali metal base in a reaction inert liquid reaction medium and the resulting alkali metal salt reacted with a reactive ester of the formula AX such as a halide, phosphate or sulfate to yield a substance of Formulas I or II wherein $R^1$ is the group A as defined.

In the following procedures temperatures are expressed in degrees Centigrade. Melting points are corrected values according to the USP method where indicated (corr.). The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versus tetramethylsilane as reference standard. The relative area reported for the various shifts corresponds to the number of hydrogen atoms in the individual substituent and the nature of the shift as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), doublet (d), triplet (t), or quadruplet (q) with coupling constant reported where appropriate. The format is NMR (solvent): δ(relative area, multiplicity, J value, and, in some instances, indicated structural characteristics). Abbreviations employed are EtOH (ethanol), HOAc (acetic acid), Ar (aromatic group), $Et_2O$ (diethyl ether), DMF (dimethylformamide), MeOH (methanol), *i*-PrOH (isopropanol), $(OEt)_3CH$ (triethyl orthoformate), Nujol (mineral oil), DMSO-$d_6$ (deuterodimethyl sulfoxide), IR (infrared), KBr (potassium bromide), EtOAc (ethyl acetate), d (decomposition). "Nujol" is a Registered Trade Mark. Others are common and have well established meanings. The infrared spectra described include only absorption wavelengths ($cm^{-1}$) having functional group identification value. Structural characteristics are noted in some instances. Unless indicated otherwise, KBr was employed as diluent for IR spectral determinations.

PROCEDURE 1

*7-Amino-2,3-dihydro-8-[(4-chlorophenyl)methyl]-6-nitrosoimidazo[1,2-a]pyrimidin-5(8H)-one.*

To a solution of 62.30 g. 0.44 mol) of 3-chlorobenzylamine in 500 ml absolute EtOH (dried over 4A molecular sieve aluminosilicate desiccant) is added 107.40 g (0.44 mol) 2-(methylthio)-2-imidazoline hydroiodide. The mixture is heated to boiling on a steam bath in an open flask and about 150 ml of the ethanol is allowed to slowly boil off over 2 hr. This solution is added while still hot to 1.76 mole of sodium ethoxide in 1650 ml absolute EtOH. To the resulting stirred, basic solution of 2-[(4-chlorophenyl)methyl]amino-2-imidazoline is then added 61.85 g (0.44 mol) crystalline (mp 129-131°) ethyl oximinocyanoacetate in portions. The bright yellow solution is refluxed for 3 hr and then cooled to room temperature. The yellow precipitate is collected, washed with *i*-PrOH, and partially air-dried. The damp sodium salt is dissolved in 2000 ml $H_2O$ and acidified with glacial HOAc. The bright pink precipitate is filtered and air-dried overnight, then oven-dried *in vacuo* at 100° to yield 103.05 g (77%) of pink powder, mp 238-241°d. Recrystallization of this material from DMF-EtOH gives red crystals, mp 241°d.

*Anal.* Found: C, 50.68; H, 3.93; N, 22.59; IR (Nujol) 1600-1700 $cm^{-1}$ (C=O, C=N), 3550 $cm^{-1}$ (NH). NMR (DMSO-$d_6$) 3.90 [4, m, $(CH_2)_2$], 5.15 (2, s, $CH_2AR$), 7.32 (4, s, Ar).

PROCEDURE 2

*7-Amino-8-[(4-chlorophenyl)methyl]-6-(formyl-amino)-2,3-dihydroimidazo[1,2-a]pyrimidin-5(8H)-one.*

A 40.50 g (0.133 mol) sample of unrecrystallized nitroso compound of Procedure 1 is dissolved in 950 ml 97% HCOOH and 25.0 g 5% Pd/C-50% $H_2O$ is added under an atmosphere of $CO_2$. The mixture is reduced on a Parr hydrogenation apparatus with a starting pressure of 50 psig. About 90% of the calculated $H_2O$ consumption occurs in <15 min with a temperature rise of 12°. The remainder is taken up during 3 hr and the temperature returns to that of the room. The catalyst is filtered and the resulting colorless solution concentrated *in vacuo* to a thick syrup. The syrup dissolves in 500 ml $H_2O$ and is neutralized with concentrated $NH_4OH$ with cooling. The off-white solid is filtered and air-dried to yield 41.90 g (98%), mp 272-275°d. Recrystallization from MeOH-*i*-PrOH gives white crystals, mp 275.0°d (corr.).

*Anal.* Found: C, 52.74; H, 4.46; N, 22.01. IR (Nujol) 3420 $cm^{-1}$ (NH), 3340, 3200 $cm^{-1}$ ($NH_2$), 1680, 1620, 1580 $cm^{-1}$ :formamide, lactam, C=N). NMR (DMSO-$d_6$) 8.38-7.72 :2, multiple signals for N*H*C*H*O conformers), 4.00 [4, m, $(CH_2)_2$], 5.90 (2, s, $CH_2AR$), 7.25 (4, s, Ar).

PROCEDURE 3

*4-[(4-Chlorophenyl)methyl]-6,7-dihydro-3H-imidazo[1,2-a]purin-9(4H)-one.*

A suspension of 45.88 g (0.14 mol) of formylamino derivative of Procedure 2 in a mixture of 130 ml acetic anhydride (1.4 mol) and 65 ml $(OEt)_3CH$ (0.39 mol) is refluxed for 5 hr (a solution forms after 30 min). Concentration *in vacuo* to about 1/4 of the original volume produces an oil which dissolved in 300 ml $H_2O$). The mixture is treated with charcoal and filtered, and the clear filtrate neutralized with conc $NH_4OH$. The white precipitate is filtered and oven-dried *in vacuo* to yield 28.06 g (66%) off-white solid, mp 285-290°. Recrystallization from DMF-*i*-PrOH gave off-white crystals, mp 289-293° :corr, mp 284.0-285.0°). If this material is shown by NMR to contain solvated DMF, it may be removed by stirring the suspended solid in $Et_2O$, and then redrying.

*Anal.* Found: C, 55.96; H, 4.40; N, 23.16. IR (Nujol) 1620 $cm^{-1}$ (C=N), 1680 $cm^{-1}$ (C=O). NMR (DMSO-$d_6$, ppm) 3.84 [4, m, $(CH_2)_2$], 5.10 (2, s, $CH_2AR$), 7.50 (4, s, Ar), 7.91 (1, s, C*H*).

The hydrochloride salt of the product of Procedure 3 was prepared by dissolving 21.7 g of this material in 75 ml of 3*N* HCl. Dissolution was not complete when a white solid commenced to precipitate. Water, 100 ml, was added and the mixture was heated to dissolve the precipitate. The solution was treated with decolorizing carbon and filtered. Isopropanol, 150 ml, was added to the warm filtrate and the product precipitated on cooling. It was collected, dried in a vacuum oven at 80° overnight, yield 17.05 g, mp 249.0-250.0°d (corr.).

*Anal.* Found: C, 49.75; H, 3.83; N, 20.92.

PROCEDURE 4

*Pyrolytic method for the product of procedure 3.*

A slurry of 7.20 g (0.022 mol) of the product of Procedure 2 in a small volume of DMF was inserted in an oil bath at 260°. The DMF evaporated rapidly, and the residual cake was heated 12 min with constant agitation. The residual light-brown solid, mp 280-285°, weighed 6.36 g. (93%). Recrystallization from DMF gave material identical to that obtained by Procedure 3.

Various amines were substituted for 4-chlorobenzylamine in the method of Procedure 1 and the resulting nitrosoimidazopyrimidinones were converted according to Procedure 2 to the corresponding formyl-aminoimidazopyrimidinones which were then converted according to either Procedure 3 or Procedure 4 to one of the products of the present invention. Characterizing data and preparative information relative to these products are listed in the following table.

PROCEDURES 5-13

*6,7-Dihydroimidazo[1,2-a]purin-9-(4H)-ones of Formula I, n=1, $R^1$, $R^2$, $R^6$, $R^7$ = H*

| No. | $R^4$ | *m.p. °C (corr.)* | *Method* | *Yield* | *Recryst. Solvent* | *Elemental Analysis* | *NMR* | *IR* |
|---|---|---|---|---|---|---|---|---|
| 5 | 3-chlorobenzyl | 262.0-267.0 | Proc 3. | 27% | DMF | C 56.05<br>H 4.14<br>N 23.20 | (DMSO-$d_6$) 3.89(4,m)<br>5.15(2,s), 7.48(4,m),<br>7.98(1,s), 13.5(1,bs) | 760, 800, 1400<br>1550, 1625, 1700,<br>2600, 2880, 2975,<br>3110 |
| 6 | 2-chlorobenzyl | 292.0-293.0 | Proc. 3 | 54% | DMF | C 55.60<br>H 4.01<br>N 23.21 | (DMSO-$d_6$) 3.84(4,m)<br>5.20(2,s), 7.42(4,m),<br>8.01(1,s), 13.4(1,bs) | 756, 1295, 1360,<br>1550, 1620, 1700,<br>2880, 2960, 3100 |
| 7 | 3,4-dichlorobenzyl | 279.0-280.0 | Proc. 3 | 96% | MeOH | C 50.09<br>H 3.29<br>N 20.53 | (DMSO-$d_6$) 3.86(4,m),<br>5.10(2,s), 7.54(3,m),<br>7.89(1,s), 13.4(s,bs) | 770, 1140, 1305,<br>1440, 1480, 1560,<br>1635, 1700, 2900,<br>3140 |
| 8 | 4-fluorobenzyl<br>HCl salt | 296.0-298.0<br>251.0-252.0 | Proc. 4 | 71% | DMF<br>MeOH-*i*-PrOH | C 58.98<br>H 4.30<br>N 24.41 | (DMSO-$d_6$ 3.85(4,m),<br>5.14(2,s), 7.49(4,m),<br>8.01(1,s), 13.5(1,bs) | 835, 1220, 1450,<br>1550, 1625, 1690,<br>3130 |
| 9 | 2-methoxybenzyl | 228.5-233.5 d* | Proc. 4 | 34% | 1*N* HCl-$NH_4OH$ | C 58.62<br>H 5.18<br>N 23.23 | (DMSO-$d_6$) 3.79(3,s),<br>4.15(4,m), 5.39(2,s),<br>7.20(4,m), 8.22(1,s) | 755, 1240, 1292,<br>1490, 1550, 1610,<br>1700, 2600, 3130 |

| No. | $R^4$ | m.p.°C (corr.) | Method | Yield | Recryst. Solvent | Elemental Analysis | NMR | IR |
|---|---|---|---|---|---|---|---|---|
| 10 | 2-pyridylmethyl | 258.0-260.0* | Proc. 4 | 50% | DMF | C 56.28<br>H 4.38<br>N 29.95 | (DMSO-$d_6$) 3.80(4,m), 5.18(2,s), 7.24(2,m), 7.76(1,m), 7.85(1,s), 8.70(1,m) | 796, 1360, 1472, 1560, 1610, 1705, 2980, 3130, 3520 |
| 11 | 2-(3,4-dimethoxy-phenyl)ethyl | 218.0-224.0* | Proc. 4 | 52% | 1*N* HCl-$NH_4OH$ | C 54.80<br>H 5.68<br>N 18.55 | (DMSO-$d_6$) 2.90(2,m), 3.78(6,s), 3.90(9,m), 4.70(2,m), 6.90(3,m), 7.98(1,s) | 760, 1265, 1520, 1630, 1690, 2970, |
| 12 | 2-(phenoxy)ethyl | 223.5-224.5 | Proc. 3 | 58% | MeOH | C 60.56<br>H 5.09<br>N 23.48 | (DMSO-$d_6$) 3.90(4,m), 4.37(4,m), 7.26(5,m), 8.04(1,s) | 690, 752, 1240, 1500, 1625, 1705, 2960, 3060, 3120 |
| 13 | isobutyl | 230.5-231.5 | Proc. 4 | 34% | *i*-PrOH | C 56.53<br>H 6.54<br>N 29.84 | (DMSO-$d_6$) 0.92(6,d 6.5 Hz), 2.32(1,m), 3.82(6,m), 7.90(1,s) | 765, 895, 1300, 1436, 1550, 1620, 1700, 2970 |

PROCEDURE 14

*4-[(4-Chlorophenyl)methyl]-2-ethyl-6,7-dihydro-3H-imidazo[1,2-a]purin-9(4H)-one.*

A mixture of 25.00 g (0.078 mol) of the product of Procedure 2 and 50 ml dry pyridine in 50 ml (0.388 mol) of propionic anhydride was heated at reflux for 3 hr. Upon cooling, a white solid precipitated. $CH_3CN$ was added, and the white solid filtered and air-dried to give crystals, mp 278.0-279.0° (corr.). The material may be recrystallized from DMF-*i*-PrOH. NMR (DMSO-$d_6$): 1.22 (3, t, 7.5 Hz), 2.67 (2, 9, 7.5 Hz), 3.98 (4, m, 5.08 (2, s), 7.43 (4, m, 11.3 (1, bs). IR: 756, 805, 1295, 1510, 1630, 1695, 3050, 3100, 3160.

*Anal.* Found: C, 58.28; H, 4.76; N, 21.34.

PROCEDURE 15

*4-[(4-Chlorophenyl)methyl]-6,7-dihydro-2-methyl-3H-imidazo[1,2-a]purin-9(4H)-one.*

The method of Procedure 14 was repeated with the substitution of acetic anhydride for propionic anhydride. The resulting product was obtained as a cream-colored solid, mp 311.5-313.5° (corr.), recrystallized from DMF-*i*-PrOH.

*Anal.* Found: C, 56.72; H, 4.36; N, 22.35. NMR (DMSO-$d_6$) 2.36 (3,s), 3.91 (4,m), 5.20 (2,s), 7.90 (4,m). IR 755, 804, 1020, 1294, 1510, 1630, 1690, 3050, 3160.

PROCEDURE 16

*4-[(2-Chlorophenyl)methyl]-2-(1-methylethyl)-6,7-dihydro-3H-imidazo[1,2-a]purin-9(4H)-one.*

2-Chlorobenzylamine is substituted for 4-chlorobenzylamine in the process of Procedure 1 and the resulting nitrosoimidazopyrimidinone is converted to the corresponding formylamino compound according to the method of Procedure 2, and the resulting product is then reacted with isobutyric anhydride in a mixture of isobutyric anhydride and pyridine according to the method of Procedure 14 to give the desired product. Obtained as a fluffy white crystalline solid, mp 249.5-255.0° after recrystallization from a mixture of chloroform and acetonitrile.

*Anal.* Found: C, 59.34; H, 5.54; N, 20.22. NMR (DMSO-$d_6$) 2.10 (6,d, 6.5Hz), 2.94 (2, septet, 6.5 Hz), 3.84 (4,m), 5.12 (2,s), 7.30 (4,m). IR 760, 1300, 1505, 1626, 1692, 3180.

PROCEDURE 17

*2-Bromo-4-[(4-Chlorophenyl)methyl]-6,7-dihydro-3H-imidazo[1,2-a]purin-9(4H)-one Hydrobromide.*

Bromine, 1.60 g (0.010 mol), was added to a solution of 2.00 g (0.0066 mol) of the product of Procedure 3 in 10 ml HOAc and the resulting solution heated on a steam bath for 10 min. Yellow flakes precipitated and were filtered and air-dried to give 3.29 g solid, mp 212°d. Heating a suspension of the material in $CH_2CN$ gave a white powder, mp 248°d. Recrystallization from DMF–$CH_3CN$ gave fine, white needles, mp 228.5-229.5°d. (corr.).

*Anal.* Found: C, 36.48; H, 2.92; N, 15.01.

PROCEDURE 18

*7-Amino-8-benzyl-2,3-dihydro-6-nitrosoimidazo-[1,2-a]pyrimidin-5(8H)-one.*

The method of Procedure 1 is repeated with the substitution of benzylamine for 4-chlorobenzylamine. Product melting point 242°d., 68% yield, recrystallized from DMF.

PROCEDURE 19

*7-Amino-2,3-dihydro-6-formylaminoimidazo[1,2-a]pyrimidin-5(8H)-one.*

The method of Procedure 2 is applied to the product of Procedure 18 to yield this product, mp 268°d, yield 40%. The product was not recrystallized.

PROCEDURE 20

*6,7-Dihydro-2-(1-methylethyl)-4-(2-methylpropionyl)-3H-imidazo[1,2-a]purin-9(4H)-one.*

The method of Procedure 14 was applied to the product of Procedure 19 with the substitution of isobutyric anhydride for the priopionic anhydride specified in Procedure 14. The product was obtained in 35% yield, mp 271.0-273.0° (corr.) after recrystallization from isopropanol.

*Anal.* Found: C, 58.50; H, 6.25; N, 24.39. NMR (DMSO-$d_6$) 1.20 (6,d), 1.34 (6,d), 3.00 (1,m), 4.10, (5,m), 13.2 (1, bs). IR 780, 1250, 1275, 1365, 1410, 1540, 1580, 1700, 2980, 3200.

PROCEDURE 21

*7-Amino-8-[(4-fluorophenyl)methyl]-6-(formylamino)-2,3-dihydroimidazo-[2,3-a]pyrimidin-5(8H)-one.*

7-Amino-2,3-dihydro-8-[(4-fluorophenyl)methyl]-6-nitrosoimidazo[1,2-*a*]pyrimidin-5(8H)-one is prepared by the method of Procedure 1 with substitution of 4-fluorobenzylamine for 4-chlorobenzylamine which is used in that example. To the resulting product 9.79 g (0.034 mol), mp 223.5-225.5°d (corr.) in 100 ml of 97% HCOOH at room temperature is added 15.00 g (0.086 mol) $Na_2S_2O_4$ in portions over about 5 min. The solution turns from dark purple to light yellow during the resulting exothermic reaction, and some yellow precipitate forms. The mixture is stirred for 10 minutes, then concentrated *in vacuo* to about 25 ml. The residual is dissolved in 150 ml $H_2O$, filtered, and neutralized with concentrated $NH_4OH$. The white precipitate is collected, slurried in hot MeOH, and filtered. Oven drying *in vacuo* yields 9.25 g (90%) white solid, mp 248-250°. Recrystallization from MeOH yields white crystals, mp 262°d.

*Anal.* Found: C, 55.20; H, 4.62; N, 22.87.

The formylamino compound produced by Procedure 21 was converted according to the method described in Procedure 4 to yield a product identical to that produced in Procedure 8.

PROCEDURE 22

*7-Amino-8-(phenylmethyl)-2,3-dihydro-6-(formylamino)imidazo[1,2-a]pyrimidin-5(8H)-one.*

The method of Procedure 21 is applied to the product of Procedure 18 to prepare this material in 86% yield, mp 248-250° after recrystallization from DMF-*i*-PrOH.

*Anal.* Found: C, 58.84; H, 5.38; N, 24.31. NMR (DMSO-$d_6$) 3.79 (4,m), 5.30 (2,s), 6.66 (2,bs), 7.50 (5,m), 8.36 (1,s), 8.82 (1,s). IR 700, 740, 1305, 1500, 1580, 1612, 1655, 3200, 3320, 3400.

PROCEDURE 23

*4-(Phenylmethyl)-6,7-dihydro-3H-imidazo[1,2-a]purin-9(4H)-one.*

The product of Procedure 22 is substituted as formylamino starting material in the method of Procedure 3. The product is obtained in 64% yield as a light yellow crystalline solid, mp 262-264° (corr.) after recrystallization from DMF-*i*-PrOH.

*Anal.* Found: C, 62.57; H, 5.15; N, 26.13; NMR (DMSO-$d_6$) 3.88 (4,m), 5.16 (2,s), 7.45 (5,m), 8.00 (1,s). IR 715, 764, 1300, 1435, 1550, 1620, 1700, 3150.

PROCEDURE 24

*1-Butyl-4[(4-chlorophenyl)methyl]-6,7-dihydroimidazo[1,2-a]purin-9(4H)-one Hydrochloride.*

To a stirred suspension of 1.77 g (0.0059 mol) the product of Procedure 3 in 20 ml dry DMF was added 0.27 g (0.0065 mol) NaH (57% mineral oil dispersion). When dissolution was complete, 0.69 g (0.0065 mol) n-butyl bromide was added, and the mixture was heated at 100° for 3 hr. Water (200 ml) was added, and the aqueous portion decanted from the precipitated gum. The gum was dissolved in 100 ml 1 *N* HCl and was filtered. The resulting yellow solution was made basic with NH4OH. and the resulting gum was taken up in *i*-PrOH. The *i*-PrOH solution was acidified with ethanolic HCl and allowed to evaporate. The solid residue was recrystallized from $CH_3CN$-EtOAc to give 0.65 g (28%) pale-yellow crystals, mp 223-225° (corr. mp 205.5-206.5°d). IR: 770, 1310, 1480, 1500, 1608, 1660, 1720, 2710, and 3110. NMR ($CDCl_3$): 0.83 (3,t, 6.2 Hz), 1.27 (2,m), 1.73 (2, m), 4.28 (6, m), 5.88 (2, s), 7.39 (2, m), 8.04 (1, s).

*Anal.* Found: C, 54.48; H, 5.56; N, 17.84.

PROCEDURE 25

*4-[(4-Chlorophenyl)methyl]-6,7-dihydro-3H-imidazo[2',1':5,6)v-triazolo[4,5-d]pyrimidin-9(4H)-one.*

A solution of 1.00 g (0.0033 mole) of the product of Procedure 1 in 50 ml 1 *N* HCl was hydrogenated over 0.50 g. 10% Pd/C. The catalyst was filtered, and the filtrate cooled to 0°. A solution of 0.24 g. :0.0035 mole; $NaNO_2$ in 2 ml $H_2O$ was added in one portion, and the solution was stirred at 25°C. for 30 minutes. The solution was concentrated *in vacuo* to a solid residue which was slurried in MeOH and filtered. The filtrate was concentrated *in vacuo*, and the crystalline residue slurried in $CH_3CN$ and filtered to yield 0.60 g pink crystals, mp 252°d. The material was dissolved in 1 *N* NaOH and neutralized with HOAc. The white solid was filtered and air-dried to yield 0.50 g (50%), mp > 300.0°. IR: 770, 810, 1305, 1495, 1585, 1640, 1720, and 2700. NMR (DMSO-$d_6$ + $CF_3CO_2H$): 4.26 (4, m), 5.57 (2, s), 7.79 (5, m).

*Anal.* Found: C, 51.30; H, 4.02; N, 27.65.

Various nitrosoimidazolopyrimidinones prepared as intermediates in the various procedures described herein may be converted according to Procedure 25 to the corresponding imidazotriazolopyrimidinones. Refer, for instance, to Procedures 5-13, 18, 31, and 41-43. Similarly, the 1-substituted imidazotriazolopyrimidinones may be prepared from the corresponding unsubstituted compounds by application of the methods illustrated in Procedures 24, and 32-44. Characterizing data and preparative information relative to some of these products are listed in the following table.

## PROCEDURES 26-29

*6,7-Dihydro-3H-imidazo[2'1':5,6]-v-triazolo[4,5-d] pyrimidin-9(4H)-ones of Formula II n=1, $R^1$, $R^6$, and $R^7$ = H*

| $R^4$ | mp °C (Corr.) | Yield | Recryst. Solvent | Elemental Analysis | NMR | IR |
|---|---|---|---|---|---|---|
| 3,4-dimethoxyphenethyl | *286.0-287.0* | *51%* | *1 N* NaOH-HOAc | C 55.46<br>H 5.27<br>N 24.07 | ($CF_3CO_2H$) 4.03 (6,s), 3.32 (2,m), 4.50 (6,m) 7.08 (3,m) | 775, 1305, 1520, 1580, 1650, 1725, 2700 |
| 4-fluorobenzyl | 294.0-295.0 d. | 29% | 1 *N* NaOH-HOAc | C 54.30<br>H 3.86<br>N 29.08 | (dmso-$d_6$) 4.00 (4,m) 5.21 (2,s), 7.41 (4,m) | 770, 830, 1300, 1510, 1580, 1640, 1720, 2700 |
| 3,4-dichlorobenzyl | 247.5-249.5 d. | 43% | water | | (DMSO-$d_6$) 4.21 (4,m) 5.72 (2,s), 7.85 (3,m) | 825, 1320, 1590, 1665, 1755, 2800, 3000 |
| hydrogen* | >300 | 9% | 1 *N* NaOH-HOAc | C 40.05<br>H 3.62<br>N 46.27 | (DMSO-$d_6$) 3.90 (4,m) 8.20 (1,bs) | 780, 1280, 1540, 1620, 1700, 3080, 3160 |

*pared by substitution of *o*-methoxybenzylamine in the method of Procedure 1 *wed by reduction and cyclization of that product by the method of Procedure 25; *enzylation occurred resulting in the formation of the $R^4$ hydrogen product indicated.

PROCEDURE 30

*7-Amino-2,3-dihydro-8-(2-methylpropyl)imidazo[1,2-a]pyrimidin-5(8H)-one.*

A mixture of 29.25 g (0.40 mole) isobutylamine and 48.82 g (0.20 mole) 2-(methylthio)-2-imidazoline hydroiodide in 250 ml abs. EtOH were refluxed for 2 hr. The mixture was concentrated *in vacuo* to a viscous oil, which was dissolved in 100 ml abs. EtOH and added to a solution of 18.40 g (0.80 mole) sodium and 22.62 g (0.20 mole) ethyl cyanoacetate in 1200 ml abs. EtOH. The mixture was refluxed for 3 hr, then concentrated *in vacuo* to a viscous oil. Water (400 ml) was added and a white solid slowly crystallized. The solid was filtered and air-dried to yield 35.43 g (86%), mp 235-238° (two crops). Recrystallization from $CH_3CN$ gave white crystals, mp 230.5-232.5° (corr.). NMR (DMSO-$d_6$): 0.89 (6, d, J 6.0 Hz), 2.04 (1, m), 3.68 (2, d), 3.76 (4, m), 4.38 (1,s), 7.68 (2, bs). IR: 770, 1190, 1280, 1490, 1610, 1655, 3160, and 3300.

*Anal.* Found: C, 57.75; H, 7.93; N, 27.14.

PROCEDURE 31

*7-Amino-2,3-dihydro-8-(2-methylpropyl)-6-nitrosoimidazo[1,2-a]pyrimidin-5(8H)-one.*

To a solution of 5.00 g (0.024 mole) of the product of Procedure 30 in 15 ml $H_2O$ and 4 ml HOAc (0°) was added (portionwise) 1.72 g (0.024 mole) $NaNO_2$. The mixture was stirred at 24° for 30 min, cooled to 0° and filtered to yield 4.44 g (72%) of a purple solid, mp 203-205°d.

Recrystallization from $H_2O$ provided pink needles, mp 205-207°.

*Anal.* Found: C, 45.56; H, 7.16; N, 26.93.

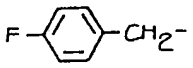
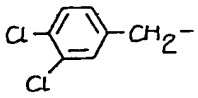
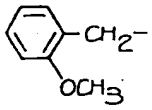
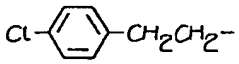
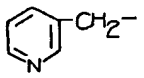
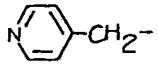
The product of Procedure 31 is then converted to the product of Procedure 13 by reduction to the corresponding formylamino compound by the method of Procedure 2 and cyclization by the method of Procedure 4.

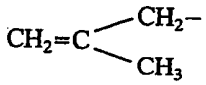
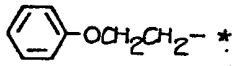
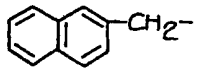
PROCEDURES 32-40

The method of Procedure 24 is applied to the product of Procedure 13 with the substitution of the following reactants for *n*-butyl bromide to yield the analogous products which are listed in the following table.

PROCEDURES 32-40

*1,R-6,7-Dihydro-4-(2-methylpropyl)imidazo[1,2-a]purin-9(4H)-ones*

| *Proc. No.* | *Reactant* | *R'* |
|---|---|---|
| 32 | 4-fluorobenzyl chloride |  |
| 33 | 3,4-dichlorobenzyl chloride |  |
| 34 | 2-methoxybenzyl chloride |  |
| 35 | 2-(4-chlorophenyl)ethyl bromide |  |
| 36 | 3-chloromethylpyridine |  |
| 37 | 4-chloromethylpyridine |  |

| Proc. No. | Reactant | $R^1$ |
|---|---|---|
| 38 | 3-bromo-2-methylpropene |  |
| 39 | 2-phenoxyethyl bromide |  * |
| 40 | 2-naphthylmethyl bromide |  |

*Yield 53%, recrystallized from $CH_3CN$, mp 228-230°. NMR ($CDCl_3$): 1.10 (6,d, 6.2 Hz), 2.40 (1,m), 4.41 (8,m), 4.83 (2,t, 6.0 Hz), 7.21 (5,m), 8.06 (1,s), 13.7 (1,bs). IR: 700, 760, 1250, 1460, 1600, 1645, 1715, 2600, 2980.
*Anal.* Found: C, 58.75; H, 6.18; N, 17.88.

PROCEDURE 41

*4-[(4-Chlorophenyl)methyl]-6,7-dihydro-6,7-dimethyl-3H-imidazo[1,2-a]purin-9(4H)-one.*

Procedure 1 is repeated with substitution of 4,5-dimethyl-2-(methylthio)-2-imidazoline hydroiodide for the 2-(methylthio)-2-imidazoline hydroidide specified. The resulting 7-amino-2,3-dihydro-2,3-dimethyl-8-[(4-chlorphenyl)-methyl]-6-nitrosoimidazo[1,2-*a*]pyrimidin-5(8*H*)-one is converted to the corresponding 6-formylamino compound by the method of Procedure 2 and the latter is converted to the desired product by the method of Procedure 4.

PROCEDURE 42

*4-[(4-Chlorphenyl)methyl]-7,8-dihydro-3H,6H-pyrimido[1,2-a]purin-10(4H)-one.*

Procedure 1 is repeated with substitution of 2-(methylthio)-3,4,5,6-tetrahydropyrimidine hydroidide for the 2-(methylthio)-2-imidazoline hydroidide specified. The resulting 8-amino-3,4-dihydro-9-[(4-chlorophenyl)methyl]-7-nitroso-2*H*,5*H*-pyrimido-(1,2-*a*)pyrimidin-6(9*H*)-one is converted to the corresponding 7-formylamino compound according to the method of Procedure 2, and the latter is then cyclized to the desired product by the method of Procedure 4.

PROCEDURE 43

*4-[(4-Chlorophenyl)methyl]-6,7,8,9-tetrahydro-3H-1,3-diazepino[1,2-a]purin-11(4H)-one.*

Procedure 1 is repeated with substitution of 2-(methylthio)-4,5,6,7-tetrahydro-1*H*-1,3-diazepine hydroiodide for the 2-(methylthio)-2-imidazoline hydroiodide specified. The resulting 9-amino-10-[(4-chlorophenyl)methyl]-8-nitroso,2,3,4,5-tetrahydro-1,3-diazepino[1,2-*a*]-pyrimidin-7(10*H*)-one is converted to the corresponding 8-formylamino compound by the method of Procedure 2, and the latter is then cyclized to the desired product by the method of Procedure 4.

PROCEDURE 44

*1,4-Di[(4-fluorophenyl)methyl]-6,7-dihydroimidazo[1,2-a]purin-9(4H)-one.*

The method of Procedure 24 is applied to the product of Procedure 8 with substitution of 4-fluorobenzyl chloride for the *a*-butyl bromide specified in Procedure 24. The product is recovered in 53% yield, recrystallized from isopropyl acetate-hexane, mp 186.0-188.0° (corr.). NMR ($CDCl_3$): 4.03 (m, 4), 5.25 (s, 2), 5.45 (s, 2), 7.34 (m, 8), and 7.57 (s, 1). IR: 760, 775, 834, 1230, 1520, 1648, and 1690.
*Anal.* Found: C, 63.76; H, 4.54; N, 17.50.

PROCEDURE 45

*4-[(4-Chlorophenyl)methyl]-2-trifluoromethyl-6,7-dihydro-3H-imidazo[1,2-a]purin-9(4H)-one.*

A solution of 25.0 g. (0.078 mol) of the product of Procedure 2 in 50 ml. of dry pyridine is prepared and chilled in an ice bath. Trifluoroacetic anhydride, 50 ml (0.355 mol) is then carefully added dropwise. The mixture is then treated as described in Procedure 14 for preparation and recovery of the desired product.

PROCEDURE 46

*6,7-Dihydro-9-imino-4-(2-methylpropyl)-3H,4H-imidazo[1,2-a]purine.*

Procedure 30 is repeated with substitution of 0.2 mol of malonitrile for the ethyl cyanoacetate specified in that example. The resulting 7-amino-2,3-dihydro-5-imino-8-(2-methylpropyl)-8*H*-imidazo[1,2-*a*]pyrimidine is then converted to the 6-nitroso compound by the method of Procedure 31, and the latter is reduced and formylated by the method of Procedure 2, and cyclized by the method of Procedure 4 to yield the desired product.

PROCEDURE 47

*4-[(4-Chlorophenyl)methyl]-6,7-dihydro-9-imino-3H,4H-imidazo[2',1':5,6]-v-triazolo-[4,5-d]pyrimidine.*

Procedure 1 is reeated with the substitution of oximinomalonitrile for the ethyl oximinocyanoacetate specified. The resulting 7-amino-2,3-dihydro-8-[(4-chlorophenyl)methyl]-5-imino-6-nitroso-8*H*-imidazo-1,2-*a*]pyrimidine is then converted to the desired product by the method of Procedure 25.

PROCEDURE 48

*2-Azido-4-[(4-chlorphenyl)methyl]-6,7-dihydro-3H-imidazo[1,2-a]purin-9(4H)-one.*

The product of Procedure 17, 1.31 g (0.0028 mol), is dissolved in 10 ml. DMF and 0.65 g (0.01 mol) of $NaN_3$ is added and the mixture heated at 100° for 1 hr. The crude product is recovered from the reaction mixture by dilution with 50 ml. of $H_2O$, yield 0.45 g. This material is dissolved in the minimum volume of DMF, 25 ml $CH_3CN$ is added, the precipitate removed by filtration, and filtrate diluted with 50 ml of $H_2O$ to yield the desired product, mp 200-212° d. IR: 2175, characteristic of the azido group.

PROCEDURE 49

*4-[(4-Chlorphenyl)methyl]-2-cyano-6,7-dihydro-3H-imidazo[1,2-a]purin-9(4H)-one.*

The method of Procedure 48 is repeated with substitution of NaCN for $NaN_3$.

PROCEDURE 50

*2-Dibutylamino-4-[(4-chlorphenyl)methyl]-6,7-dihydro-3H-imidazo[1,2-a]purin-9(4H)-one.*

The method of Procedure 48 is repeated with the substitution of dibutylamine for $NaN_3$.

When lower boiling amines such as ethylamine, or ammonia are substituted in Procedure 50 to yield a 2-loweralkylamino- or a 2-amino compound, the process is carried out in a closed vessel under pressure to afford the necessary reaction temperature. Higher boiling precursor amines such as benzylmethylamine may be employed with subsequent hydrogenolysis of the benzyl group to yield, for instance, the 2-methylamino compound.

PROCEDURE 51

*Solution for injection.*

The following ingredients are dissolved in sufficient water for injection to make 1 liter and the solution is filtered through a membrane filter having a pour size of 0.5 micrometers.

| *Ingredient* | *Amount* |
|---|---|
| Product of Procedure 27 | 0.2-5.0 g. |
| Sodium Chloride, q.s. isotonic | |
| tris(hydroxymethyl)aminomethane buffer, q.s., pH 8.5 | |

The filtered solution is filled into clean sterile ampules and flame sealed followed by sterilization in an autoclave.

PROCEDURE 52

*Tablets for oral ingestion.*

The following ingredients are blended in the dry state in a twin-shell blender and compressed on a tablet press using an 11/32 inch die and concave punches.

| *Ingredient* | *Amount* |
|---|---|
| Product of Procedure 3 | 50.0 g. |
| Sucrose, pregranulated for direct compression | 210.0 g. |
| Corn starch | 6.0 g. |
| Microcrystalline cellulose | 40.0 g. |
| Magnesium stearate | 1.0 g. |

This batch size is for 1,000 tablets and provides a tablet weighing 370 mg. supplying 50 mg. of active ingredient per tablet. Tablets containing from 25 to 200 mg. of active ingredient may be made employing the same ingredients but adjusting the weight and tablet size appropriately.

PROCEDURE 53

*Power for inhalation.*

The following ingredients are blended aseptically and filled into hard gelatin capsules, each containing 50 mg. of the mixture providing 25 mg. of the active ingredient.

| *Ingredient* | *Amount* |
|---|---|
| Product of Procedure 4, micronized | 25.0 g. |
| Lactose powder | 25.0 g. |

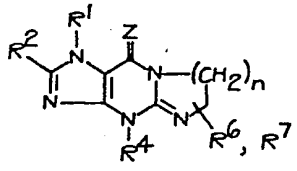
The foregoing is sufficient for 1,000 capsules. These capsules are suitable for dispensing the powder into the inspired air stream μ

| *Ingredient* | *Amount* |
|---|---|
| Product of Procedure 4, micronized | 25.0 g. |
| Lactose powder | 25.0 g. |

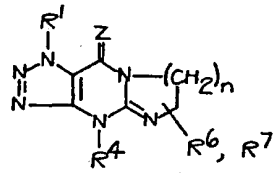
The foregoing is sufficient for 1,000 capsules. These capsules are suitable for dispensing the powder into the inspired air stream using a breath actuated device. Appropriate adjustments of the composition can be made to given capsules containing 0.5 to 40 mg. of active ingredient.

WHAT WE CLAIM IS:

1. A compound selected from



*Formula I*



*Formula II*

wherein

$R^1$ is hydrogen or the group A wherein A is alkyl, or alkenyl each having up to 8 carbon atoms, pyridylmethyl, aralkyl having 7 to 12 carbon atoms, substituted aralkyl having 7 to 12 carbon atoms, aryloxyalkyl having 8 to 12 carbon atoms, or substituted aryloxyalkyl having 8 to 12 carbon atoms wherein each of said substituted aralkyl, and substituted aryloxyalkyl groups contains 1 or 2 ring substitutents selected from halogen, alkoxy, and alkyl, and each of said alkoxy and alkyl groups contains up to 6 carbon atoms,

$R^2$ is hydrogen, trifluoromethyl, halogen, azido, cyano, amino, or alkylamino, dialkylamino or alkyl wherein said alkyl groups have up to 8 carbon atoms,

$R^4$ is hydrogen, alkyl or alkenyl each having up to 8 carbon atoms, pyridylmethyl, alkanoyl or alkenoyl each having up to 8 carbon atoms, aroyl having 7 to 10 carbon atoms, substituted aroyl having 7 to 12 carbon atoms, aralkyl having 7 to 12 carbon atoms, substituted aralkyl having 7 to 12 carbon atoms, aryloxyalkyl having 8 to 12 carbon atoms, or substituted aryloxyalkyl having 8 to 12 carbon atoms wherein each of said substituted aroyl, substituted aralkyl, and substituted aryloxyalkyl groups contains 1 or 2 ring substituents selected from halogen, alkoxy, and alkyl, and each of said alkoxy and alkyl groups contains up to 6 carbon atoms,

$R^6$ and $R^7$ represent carbon attached ring substituents and are selected from hydrogen, methyl, and ethyl,

n is the integer 1, 2, or 3, and

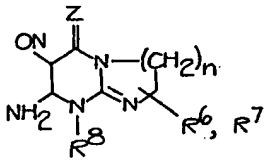
Z is oxo or imino,

and the pharmaceutically acceptable acid addition salts of the foregoing compounds, and the pharmaceutically acceptable metal, ammonium, and amine salts of the foregoing compounds wherein $R^1$ is hydrogen.

2. 4-[(4-chlorophenyl)methyl]-6,7-dihydro-3*H*-imidazo[1,2-*a*]-purin-9(4*H*)-one.

3. 4-[(4-chlorophenyl)methyl]-6,7-dihydro-3*H*-imidazo[1,2-*a*]purin-9(4*H*)-one hydrochloride.

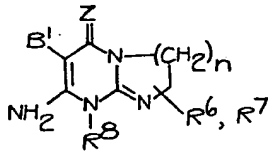
4. The process for preparing a compound as defined in Claim 1 comprising reducing a *compound having the Formula III'*



*III'*

wherein

Z, $R^6$ and $R^7$ and n are as defined in Claim 1 and $R^8$ is hydrogen, alkyl or alkenyl each having up to 8 carbon atoms, pyridylmethyl, aralkyl having 7 to 12 carbon atoms, substituted aralkyl having 7 to 12 carbon atoms, aryloxyalkyl having 8 to 12 carbon atoms, or substituted aryloxyalkyl having 8 to 12 carbon atoms wherein each of said substituted aralkyl and substituted aryloxyalkyl has 1 or 2 ring substituents selected from halogen, alkoxy, and alkyl and each of said alkoxy and alkyl groups contains up to 6 carbon atoms, under formylating conditions when a compound of Formula I is desired and under non-formylating conditions when a compound of Formula II is desired, to give a compound of Formula III



*III"*

where

Z, $R^6$, $R^7$, $R^8$ and n are as previously defined and wherein B' is the HCONH-group when the reduction has been carried out under formylating conditions and wherein B' is the $H_2N$-group when the reaction has been carried out under non-formylating conditions and thereafter cyclizing said compound of Formula III" (B' is $H_2N$- or HCONH-) to yield a compound of Formula I or Formula II wherein $R^4$ has the same meaning as $R^8$ and when a compound of Formula I or Formula II is desired having $R^4$ = alkanoyl, aroyl or substituted aroyl, reacting a substance of Formula I or Formula II wherein $R^4$=H with an acylating agent capable of introducing said alkanoyl, aroyl or substituted aroyl group under conditions known for the production of amides from aromatic amines and when a compound of Formula I is desired having $R^2$ = halogen, treating a compound of Formula I wherein $R^2$ = halogen with a halogenating agent known to be suitable for introducing a halogen atom into an aromatic compound, and when a compound of Formula I or Formula II wherein $R^1$ is the group A, as previously defined, converting a compound of Formula I or Formula II wherein $R^1$ is hydrogen to an alkali metal salt by treatment thereof with a strong alkali metal base and reacting the resulting alkali metal salt with a reagent of Formula AX wherein A is as defined in Claim 1 and X is a reactive ester group, and when a pharmaceutically acceptable acid addition salt of a compound having Formula I or Formula

II is desired, reacting a compound of Formula I or Formula II with a pharmaceutically acceptable acid, and when a pharmaceutically acceptable metal, ammonium or amine salt of a compound having Formula I or Formula II is desired, reacting a compound of Formula I or Formula II wherein $R^1$ = hydrogen with a pharmaceutically acceptable base.

5. A process according to Claim 4 wherein the compound of Formula III′ is prepared by condensation of malonitrile, oximinomalonitrile or a lower alkyl ester of cyanoacetic acid or oximinocyanoacetic acid, respectively, with a 2-$R^8$NH-1,3-diazacycloalk-2-ene wherein $R^8$ is as defined in Claim 4 and thereafter introducing the nitroso group by reaction of the product with nitrous acid when cyanoacetic ester or malonitrile is used as reactant.

6. A process according to Claim 4 or 5 wherein said compound III′ is reduced to a compound III″ (where B′ is HCONH−) by reacting said nitroso compound III′ with at least two molecular proportions of sodium dithionite in concentrated aqueous formic acid as reaction medium.

7. A process for preparing a compound according to Claim 1 substantially as hereinbefore described.

8. A compound whenever prepared by the process of any one of Claims 4 to 7.

9. A compound according to Claim 1 substantially as described herein and exemplified.

10. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 3 or 8 and a pharmaceutical diluent or carrier.

11. A pharmaceutical composition comprising a compound of Claim 2 or Claim 3 and a pharmaceutical diluent or carrier.

12. A method for inhibiting the immediate hypersensitivity reaction in a sensitive non-human mammal which comprises administering to said mammal a non-toxic effective hypersensitivity reaction inhibiting dose of a compound of any one of Claims 1 to 3, 8 or 9.

13. A method for relieving bronchospasm in a non-human mammal suffering therefrom which comprises administering to said mammal a non-toxic bronchodilator effective dose of a compound claimed in any one of Claims 1 to 3, 8 or 9.

14. A method for exerting a vasodilator effect in a non-human mammal which comprises administering to a mammal in need of vasodilitation a non-toxic vasodilator effective dose of a compound claimed in any one of Claims 1 to 3, 8 or 9.

15. A compound of Formula I in accordance with Claim 1, wherein $R^1$ and $R^2$ are each hydrogen, $R^4$ is 4-chlorobenzyl, $R^6$ and $R^7$ are each methyl, n is 1, and Z is oxo.

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